REMARKS

Reconsideration of this application, as amended, is respectfully requested. Claims 1, 2, 4-27, and 29-31 were pending in this application. Claim 1 has been amended and new claims 34 and 35 introduced. These amendments are made without prejudice or disclaimer and do not include any new matter. Applicants reserve the right to prosecute any cancelled or otherwise unclaimed subject matter is this or another application. Consideration and entry of this amendment is respectfully requested.

REJECTIONS UNDER 35 U.S.C. 103(a)

A. Claims 1, 2, 4-17 and 20

Claims 1-2, 4-17, and 32-33 stand rejected under 35 U.S.C. 103(a) over Hurpin (1998) in view of Hodge (1997), Rice (U.S. Pat. No. 6,127,116 (1997)), and Lehner (1999). Applicants respectfully traverse these rejections as indicated below.

Hurpin is alleged to demonstrate that administration of antigen to a lymphatic tissue may be a successful route of administration. As Hurpin does not teach a prime-boost regimen, Hodge is cited as teaching the use of two different poxviral vectors to generate an immune response. As neither of these references teaches direct intranodal administration of antigen, both Rice and Lehner are cited. Rice is alleged to teach direct intranodal administration as a preferred immunization route. Lehner is alleged to provide a reasonable expectation of success in using intranodal immunization by demonstrating success using their "targeted iliac lymph node" or "TILN" technique. As described below, the Applicants do not believe this combination of references renders the instantly claimed method obvious.

With respect to Hurpin, the Examiner alleges in this Office Action:

> Specifically, Hurpin et al. teaches that whereas administration to lymphatic tissue, such as the spleen, generated substantial antigen specific CTL response, subcutaneous administration of vaccinia encoding p53 failed to generate antigen specific CTL (Hurpin, et al. pages 210-211). (Office Action, p. 3)
>
> As previously noted, the spleen is a lymphatic tissue. Further, as discussed above, Hurpin et al. shows that direct administration to a lymphatic tissues generates substantially

> greater immune responses than subcutaneous administration. In fact, Hurpin et al., like applicant, shows that subcutaneous administration failed to generate antigen specific CTL against p53. Thus, Hurpin shows that administration to lymphatic tissue can induce antigen specific immunes greater than that induced by subcutaneous administration, which can be further increased by subsequent administrations to lymphatic tissue. (Office Action, p. 4)

However, with regard to "lymphatic tissue", Hurpin actually states:

> Intrasplenic administration also induced CTLs. (Hurpin, et al. Abstract, p. 208)
>
> For direct intrasplenic administration, mice were anesthetized and shaved, and 20 µl were delivered through the abdominal wall into the spleen. (Hurpin, et al., pages 209)
>
> However, direct intrasplenic administration, which has recently been reported to be extremely potent for inducing cellular responses to transfected fibroblasts[32], did induce CTLs, although it was not clearly superior to the intravenous route. (Hurpin, et al., pages 210-211)
>
> Since we presume that targeting to the spleen, which is rich in APCs and cytokines, is at least in part responsible for the immunogenicity of the intravenous route, it is interesting that direct intrasplenic administration also induced a CTL response. (Hurpin, et al., page 213)

As shown by the quoted passages, Hurpin does not teach "administration to lymphatic tissue, such as the spleen", as alleged by the Examiner, but only teaches administration to the spleen. In fact, Hurpin does not even mention "lymphatic tissue" or lymph nodes. It is understood that the spleen is a lymphatic tissue but only intranodal administration is instantly claimed. The Examiner's allegation that Hurpin teaches vaccine delivery "to lymphatic tissue, whether spleen or lymph node" is an incorrect characterization of what the reference actually discloses. With regard to lymphatic tissue, Hurpin teaches intrasplenic administration and nothing more. Applicants are fully cognizant that these rejections rest on the combination of Hurpin, Hodge, Rice and Lehner, and that an argument as to why each reference would not individually render the

pending claims obvious is improper. However, at least one of the Examiner's factual findings regarding at least one of the references in the combination (e.g., Hurpin) is incorrect. In view of this error, Applicants respectfully maintain that rejections relying upon the Examiner's characterization of Hurpin are improper and should be withdrawn.

Regarding Lehner's 1994 paper, previously cited by Applicants to further characterize Lehner's method, the Examiner notes that the 1994 paper "states that the iliac lymph nodes are located 2-4 cm subq...." Appilcants do not disagree with this statement. "Subcutaneous" is typically understood by those of skill in the art to mean, e.g., just under the skin. As Lehner admittedly administered the antigen subcutaneously, and the iliac lymph nodes are found 2-4 cm therefrom, it follows that Lehner in fact administered antigen 2-4 cm from the iliac lymph nodes. In Applicants' Example 1 (Group 3), subcutaneous administration was accomplished using "four injection sites in the dorsal cervical/interscapular region", a region known to be populated with lymph nodes (see, e.g., Pond et al. J. Lipid Res., 36: 2219-2231 (1995)). It would therefore be understood by one of skill in the art that Applicant's control subcutaneous injection is in fact similar to Lehner's subcutaneous technique, although near a different group of lymph nodes. And, as shown in the Examples, Applicants' direct intranodal administration method induced much greater immune responses as compared to the control (e.g., Fig. 5). Applicants are not attempting to argue for patentability over Lehner alone, but reiterating their belief that the Examiner's reasoning regarding Lehner's role within the combination of references is improper. Accordingly, Applicants respectfully maintain that the rejections based on Lehner are improper and should be withdrawn.

Applicants further maintain their previously stated position that Rice merely mentions at col. 43, lines 43-52 that the cDNAs described therein may be incorporated into vaccines that may be administered "directly...to lymphoid tissues, e.g., lymph nodes...", and that this disclosure is insufficient. It is again pointed out that Rice's suggestion provides insufficient support for an obviousness rejection, for the reasons set forth in PharmaStem Therapeutics:

> . . . an invention would not be deemed obvious if all that was suggested "was to explore a new technology or general approach that seemed to be a promising field of experimentation, where the prior art gave only general

> guidance as to the particular form of the claimed invention or how to achieve it." PharmaStem Therapeutics Inc. v. Viacell, Inc. 491 F.3d 1342, 1364 (Fed. Cir., 2007))

Rice does nothing more than point out a particular route of administration provides absolutely no guidance whatsoever as to how to achieve it. Applicants are not attempting to argue for patentability over Rice alone, but reiterating their belief that the Examiner's reasoning regarding Rice's role within the combination of references is improper.

Applicants respectfully maintain that the Examiner has not made a proper *prima facie* showing of obviousness through the combination of Hurpin, Hodge, Lehner and Rice. Applicants do not believe Hurpin relates to "lymphatic tissue" generally but only to the spleen. Applicants further believe that neither Lehner nor Rice show administration of antigen directly into a lymph node. Accordingly, it is respectfully requested that these rejections be withdrawn. It is also noted that Applicants do not believe these rejections would apply to either of new claims 34 or 35, relating to vaccination of humans and administration of both forms of antigen to the same lymph node, respectively.

B. Claims 18-19

Claims 18 and 19 stand rejected under 35 U.S.C. 103(a) over Hurpin (1998) in view of Hodge (1997), Rice (US Pat. No. 6,127,116; 1997), and Lehner (1999) as applied to claims 1-2, 4-17 and 20 and further in view of Zaremba (1997) and Salgaller (1996). Applicants respectfully traverse these rejections as indicated below.

Applicants have discussed the deficiencies of the rejection based on the combination of the Hurpin, Hodge, Rice and Lehner references above. As described therein, Applicants do not believe that the alleged combination of references support a proper *prima facie* case of obviousness. And Applicants do not believe Zaremba's disclosure of the peptide YLSGADLNL and / or Salgaller's disclosure of the peptide YLEPGPVTV satisfy the deficiencies of the base combination of references. Accordingly, it is respectfully requested that these rejections be withdrawn.

C. Claims 21-27

Claims 21-27 stand rejected under 35 U.S.C. 103(a) over Hurpin (1998) in view of Hodge (1997), Rice (US Pat. No. 6,127,116; 1997), and Lehner (1999) as applied to claims 1-2, 4-17 and 20 and further in view of Barnett (1997). Claim 31 has been cancelled; the rejection as to this claim is therefore moot. Applicants respectfully traverse the remaining rejections as indicated below.

Applicants have discussed the deficiencies of the rejection based on the combination of the Hurpin, Hodge, Rice and Lehner references above. As described therein, Applicants do not believe that the alleged combination of references support a proper *prima facie* case of obviousness. And Applicants do not believe Barnett's alleged disclosure of a prime/boost vaccination strategy satisfies the deficiencies of the base combination of references. Accordingly, it is respectfully requested that these rejections be withdrawn.

CONCLUSIONS

Consideration and entry of this response is respectfully requested. Applicants believe the claims are now in condition for allowance, and respectfully request that a Notice of Allowance be issued as soon as possible. The Examiner is encouraged to contact the undersigned if it is believed doing so would assist in the examination of this application.

Date: October 22, 2009

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